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Circadian regulation of adipose function

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Abbreviations: ccgs, clock-controlled genes; FFAs, free fatty acids; SCN, suprachiasmatic nucleus; TGs, triglycerides; WAT, white adipose tissue

Adipose physiology shows prominent variation over the course of the day, responding to changing demands in energy metabolism. In the last years the tight interaction between the endogenous circadian timing system and metabolic function has been increasingly acknowledged. Recent work suggests that clock and adipose function go hand in hand, regulating each other to ensure optimal adaptation to environmental changes over the 24-h cycle. In this review we describe the current knowledge on the mechanistic basis of this interaction and summarize recent findings on the impact of clock dysfunction on adipose physiology and energy homeostasis.

Introduction

Adipose function shows strong variations over the course of the day. During the active phase nutrients are transported as triglycerides or glucose to white adipose tissues where they are converted and stored in lipid droplets. During the inactive—fasting—phase, triglycerides from adipose stores are released as free fatty acids to serve as energy substrates for other organs. Furthermore, adipocytes communicate with each other and with other tissues via the release of adipokine hormones, many of which show robust oscillations along the 24-h cycle. It has recently been found that many of these functions are not a mere response to external stimuli. Instead they are controlled by endogenous circadian clocks that serve to coordinate physiology and behavior with external (day) time.

Circadian Clocks: Mechanisms

Circadian clocks are characterized by two main features: sustainment and entrainment. Sustainment means that circadian clocks are capable to maintain endogenous oscillations in the absence of external information about time of the day. The endogenous period of circadian clocks under such free-running conditions only approximates 24 h (hence the term circadian, from Latin *ca. diem*—around a day). Thus, in order to be adaptive circadian clocks have to be synchronized to the external 24-h light–dark cycle every day. This process of synchronization is called entrainment and the synchronizing stimulus, which for humans and rodents is mainly light, is termed *Zeitgeber* (German for time giver).

The molecular basis of the circadian clock is an interlocked system of transcriptional-translational feedback loops[1] (**Fig. 1**). At the core, the basic helix-loop-helix transcription factors BMAL1 (ARNTL) and CLOCK activate the transcription of *Period* (*Per1–3*) and *Cryptochrome* (*Cry1–2*) genes via binding to *E-box* promoter elements. PER and CRY proteins form heterodimers and translocate back into the nucleus, where they inhibit the BMAL1/CLOCK activator complex and thereby repress their own transcription. Neuronal PAS domain protein 2 (NPAS2), a paralog of CLOCK, can sustain clock function in the absence of the CLOCK protein in some tissues.[2,3] An additional feedback loop consists of the nuclear receptors REV-ERBα/β and RORα/β/γ, which regulate the transcription of *Bmal1* via *RRE* promoter elements. BMAL1 in turn controls the transcription of REV-ERBα/β and RORα/β/γ via *E-box* elements.[4,5] A number of posttranslational mechanisms adjust the speed of the clock by regulating the stability of CRY and PER proteins via modifications such as ubiquitination or phosphorylation.[6] In addition to this core loop system there are numerous additional components and feedback systems involved, which fine tune and stabilize the clock mechanism.[7]

The molecular clockwork regulates the transcription of so-called clock-controlled genes (ccgs) many of which are characterized by *E-box* or *RRE*-elements in their promoters. 5–10% of the transcriptome of any tissue is regulated by the circadian clock and thus shows a circadian variation of expression.[8-10] The overlap of ccgs between different tissues is surprisingly small, suggesting that ccgs represent a tissue-specific output of the circadian clock. Via regulating the transcription of many rate-limiting or key components in various cellular and signaling pathways the circadian clock controls cellular physiology in a tissue-specific manner.

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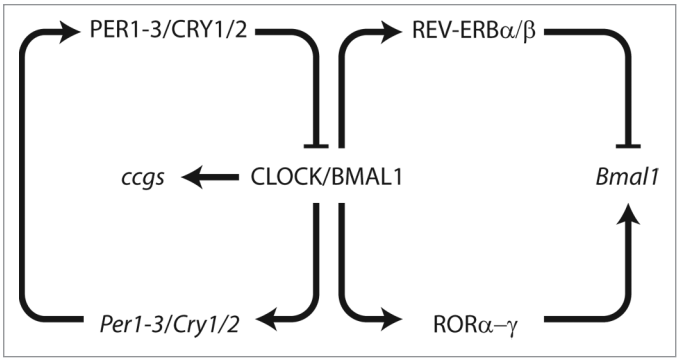

Figure 1. The mammalian molecular clockwork. Cellular clocks are based on a set of transcriptional-translational feedback loops. The transcription factors CLOCK and BMAL1 bind to E-boxes and activate *Per, Cry, ROR,* and *Rev-Erb* genes. PER and CRY proteins form complexes interfering with CLOCK/BMAL1 activity during the night phase while ROR and REV-ERB proteins regulate rhythmic *Bmal1* transcription. Clock output is achieved by binding of CLOCK/BMAL1 to clock-controlled target genes (*ccgs*).

Central and Peripheral Clocks

In mammals, a master circadian pacemaker resides in the suprachiasmatic nucleus (SCN), a paired structure in the ventral hypothalamus located directly above the optic chiasm. Destruction of the SCN in rodents results in complete loss of circadian locomotor, endocrine, and drinking rhythms.[11,12] In addition to the SCN pacemaker, so-called peripheral clocks are found in organs throughout the body.[6] Even cultured fibroblasts can express endogenous circadian rhythms for some cycles after serum shock synchronization,[13] suggesting that most if not all cells of our body contain their own endogenous circadian clock. The function of all these different clocks is currently investigated by many different labs. Transplantation and conditional gene deletion approaches are used to inactivate the clock in the tissue of interest and the behavioral, physiological, cellular, and molecular effects of such manipulations are analyzed. For example it has been shown, that the adrenal clock is involved in regulating glucocorticoid biosynthesis,[14] whereas the liver and the pancreas clocks are important for the regulation of glucose homeostasis.[15,16] The question how this complex network of clocks in different tissues is organized is still not fully understood. According to the current model the SCN, as master pacemaker, resets the phase of peripheral clocks and thus maintains a well-synchronized circadian timing system.[6] Synchronization between the different clocks is very important and disruption of synchrony between clocks can result in deleterious health effects. For example food intake at the wrong time of the day (i.e., in the inactive phase) can uncouple peripheral clocks from the SCN clock and this can impair physiology.[17] Shift work and sleep deprivation, common problems in our modern 24/7 societies, have many negative health effects including metabolic impairments such as obesity or metabolic syndrome. We and others have shown that shift work severely impairs liver function and that the circadian clock might mediate this effect, as changes in circadian transcription precede metabolic changes in a mouse model of shift work.[18] Moreover shift work impairs adipose function and the expression of many key regulators of adipose physiology is changed. Interestingly some of these effects are still detectable for several days after the end of the shift work paradigm, suggesting that circadian disruption might have longer-lasting effects than previously thought. Our data show that the circadian clock appears to be involved in mediating the effects of shift work on adipose physiology.[19] Thus the circadian clock in adipose tissues is essential for maintaining proper function of adipose physiology and, ultimately, metabolic homeostasis.

Adipose Tissue Rhythms

White adipose tissue (WAT) stores energy in form of triglycerides (TGs). During periods of extended fasting this energy can be released by breaking down TGs into free fatty acids (FFAs) and glycerol (a process termed lipolysis). Both lipogenesis (fatty acid and subsequent TG biosynthesis) and lipolysis need to be tightly regulated because excess circulating lipids as well as redundant storage of TGs promote metabolic disorders such as cardiovascular diseases and obesity. Blood levels of FFAs, TGs, and glycerol show a prominent circadian rhythm in humans and in mice[20,21] (**Fig. 2**). Importantly these rhythms do not merely reflect changes in food intake, but are regulated by the circadian clock, most likely locally via adipose transcription rhythms[20,22] and a number of key enzymes involved in both processes are under circadian control (see below).[20,23] Apart from serving as an energy store, adipose tissue is also an endocrine organ, releasing a variety of hormones (so called adipokines) which regulate appetite, energy metabolism, and inflammatory processes. The adipokines leptin, adiponectin, and visfatin are released in a circadian manner which appears endogenously regulated by the circadian timing system[24-26] (**Fig. 2**). Thus both the direct energy storage-related processes of lipolysis and lipogenesis as well as the endocrine function of adipose tissues are tightly regulated by the circadian timing system. Interestingly, shift work and sleep deprivation, which as mentioned above are associated with severe impairment of the circadian system, promote dysregulation of all these processes from lipid metabolism to adipokine release.[19,27]

Adipose Clocks and Clock-Controlled Genes

To become biologically relevant, the molecular clocks in peripheral organs such as adipose tissue have to translate their temporal information into physiological pathways. Indeed, in agreement with the microarray data from other organs (see above), transcriptomic analysis of white and brown adipose tissues revealed a large portion of rhythmically expressed genes.[28] Transcriptional oscillations of some of them, however, could be indirectly driven via rhythmic cues such as core body temperature and feeding behavior.[29,30] Nonetheless many of these cyclic genes represent ccgs, which harbor in their promoters circadian transcription factor binding elements (*E-boxes*, *RREs*—see above) and are, thus, direct targets of the circadian clock.[31] Identification of genuine (i.e., locally controlled) ccgs in a given tissue is a current challenge for circadian biologists since it would help to

better understand the interactions between tissue circadian clocks and metabolism. In particular, over the last few years genome-wide cistromic analysis was found to be an effective tool to address this issue. Chromatin immunoprecipitation with parallel DNA sequencing (ChIP-seq) performed on mouse liver samples revealed a high number of genomic loci (more than 2000) bound by BMAL1 and CLOCK in a rhythmic fashion. Many of them include genes involved in carbohydrate (such as *Glut2*, *Pck1*, and *Gys2*) and lipid metabolism (such as *Dgat2*, *Lipe*, and *Pnpla2*).[32,33] It still needs to be determined whether a similar scope of BMAL1/CLOCK targets could be found in other peripheral organs including adipose tissues. *Lipe* and *Pnpla2* transcripts are rhythmic in WAT due to direct transcriptional control by *Bmal1*. This, in turn, results in diurnal variations of triglyceride lipolysis in white adipose tissues and rhythmic release of free fatty acids (FFA) into the blood, ensuring their optimal temporal utilization as energy source and minimizing lipotoxicity effects.[20] Interestingly, a similar mechanism of clock-driven lipolysis was suggested for cardiomyocytes indicating that peripheral clocks are able to regulate local lipid metabolism.[34] In addition, the adipocyte circadian clock regulates cellular lipid influx from the blood via transcriptional control of *Lpl*, which hydrolyses FFAs from serum triglycerides and facilitates their transport through the plasma membrane.[35,36] BMAL1 binding to the promoters of *Elovl6* and *Scd1*, genes responsible for FFA elongation and desaturation, creates a rhythm in de novo synthesis of polyunsaturated FFAs.[37] BMAL1/CLOCK dimers elicit transcriptional control of *Nampt*, the main enzyme of NAD^+ regeneration passage which can be secreted as the adipokine visfatin.[26,38,39] Moreover, NAMPT can feedback on the NAD^+-dependent deacetylase SIRT1 which is present in CLOCK/BMAL1 complexes and modulates their transcriptional activity, thus coupling circadian rhythms to the metabolic state of the cell.[26,39] Another interesting aspect of BMAL1 activity in WAT includes regulation of members of the canonical *Wnt* pathway (*Wnt10a,* β-*catenin, Dvl2*) known to suppress adipogenesis.[40]

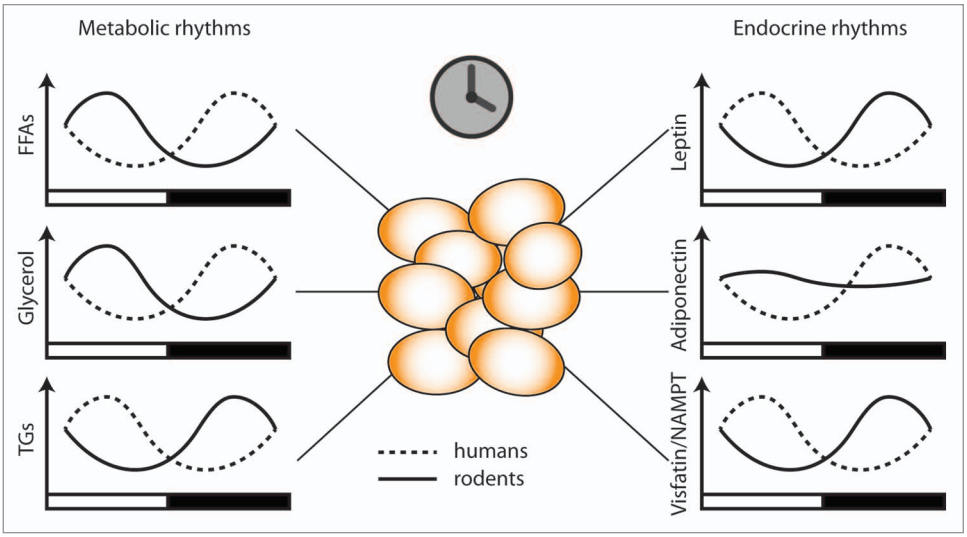

Figure 2. Dual function of white adipose tissue. Adipocytes serve as energy stores. Adipocyte clocks regulate lipid energy metabolism by regulating import of triglycerides and export of the lipolysis products free fatty acids and glycerol into the blood (left). On the other hand, adipose-secreted endocrine factors, so called adipokines, signal energy state to peripheral metabolic tissues and the brain. Some of these adipokines show prominent diurnal rhythms, both in diurnally active humans and nocturnal rodents. Black and white bars indicate night and day.

Clock genes also regulate expression of other subordinate transcription factors thereby expanding the network of ccgs and thus conveying temporal information to various metabolic pathways. In consistence with that, many members of the nuclear receptor family are enriched among BMAL1 targets in liver and show rhythmic expression profiles in both white and brown adipose tissues.[32,41] Among them are the central clock components *Rev-erb*α and β which were shown to regulate expression of genes involved in lipid metabolism in liver.[42] Moreover, activities of *Rev-erb*α/β can be modulated by different chemical ligands, thus representing a potential target for pharmacological modulation of clock and metabolic function. Cell-based studies demonstrate that activation of REV-ERBα with either synthetic or natural (heme) ligands is required for adipocyte differentiation.[43] Newly created REV-ERBα/β synthetic agonists were found to be effective for adjustment of transcriptional programs in different peripheral organs. When injected in vivo, these drugs boost energy expenditure without overt effects on food consumption. Concomitantly, a decreased expression of genes involved in the triglyceride synthesis is observed (*Dgat1*, *Dgat2*, and *Mgat1*), resulting in gradual weight loss via reduced fat deposition in WAT.[44]

*Ppar*α/γ mRNAs show maximal expression in WAT and liver at the end of the inactive phase of the day, preparing the metabolic machinery to receive food-derived lipids and deposit them as fat.[41] Indeed, many PPARγ target genes show rhythmic mRNAs profiles in WAT including *Adiponectin* and *Leptin*.[41] When secreted into the bloodstream these adipokines regulate lipid and carbohydrate metabolism and feeding behavior. Of note, the circadian clock can also modulate the PPARγ axis in a posttranslational manner via PER2, which interacts physically with PPARγ in the nucleus and inhibits its transcriptional pro-adipogenic activity.[45] Nocturnin, a circadian deadenylase that can control the stability of target mRNAs via binding to their poly(A) tails, can also regulate nuclear translocation of PPARγ and, thus, affect adipogenesis.[46] Many metabolic genes are regulated by more than one circadian modulator. Moreover, systemic metabolic signals can further impinge on adipose clock regulation. For example, insulin induces PPARγ and inhibits PCG1α signaling in adipocytes,[47,48] both of which can directly affect expression of *Bmal1*.[49,50] Moreover—at least in hepatocyte cultures—insulin has been shown to act as a resetting signal of

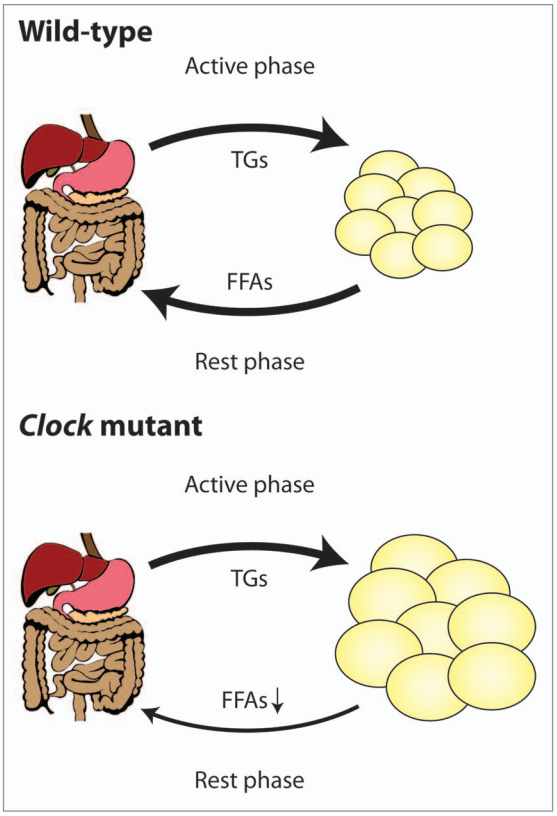

Figure 3. Rhythmic coordination of lipid energy metabolism by the circadian clock. In wild-type mice triglyceride transport to adipose tissues occurs predominantly during the night when the animals are active and eat. During the day adipose clocks promote lipid breakdown from lipid droplets and release of free fatty acids and glycerol into the blood. In *Clock* mutant animals lipid release is blocked, promoting over-accumulation of triglycerides in adipose tissues and, likely, compensatory overeating during the normal rest phase.

peripheral clocks.[51] This redundant and complementary interaction may help to more precisely time the phasing of the resulting expression rhythm and may allow for further integration of acute stimulation by non-circadian metabolic signaling pathways.

Clock Mutations and Adipose Function

Turek and colleagues have shown that mice harboring a dominant negative mutation of *Clock* (*Clock*$^{\Delta 19}$) develop obesity and severe metabolic syndrome.[52] These animals are hyperphagic and show disrupted feeding rhythms correlating with impaired expression of energy-regulatory peptides (*Grh*, *Orx*) in the mediobasal hypothalamus. *Clock*$^{\Delta 19}$ mice increase their body weight predominantly via fat deposition, leading to adipocyte hypertrophy and adiposity. While some blood lipids such as triglycerides and cholesterol are increased in *Clock*$^{\Delta 19}$ mutants, FFA and glycerol levels are remarkably downregulated.[20] This effect is inconsistent with the observed metabolic phenotype and stems from local changes in adipose tissues. *Clock*$^{\Delta 19}$ adipocytes express low levels of the lipolysis enzymes *Pnpla2* and *Lipe* and have problems efficiently mobilizing stored triglycerides (**Fig. 3**). Similarly, deletion of the *Clock* partner *Bmal1* also leads to reduced lipolysis activity and lower FFA/glycerol blood content at certain times of the day, despite the fact that *Bmal1*$^{-/-}$ mice show increased adiposity and normal food intake.[15,20,40] Thus a combination of increased body fat accompanied with reduced free fatty acid availability in the blood hints at lipid metabolism defects in adipose tissues. Mice bearing an adipose-targeted deletion of *Bmal1* show increased adiposity and body weight accompanied with impaired feeding rhythms, although, interestingly, their overall food intake is normal. The authors conclude that the adipocyte clock via the control of long-chain unsaturated FFA production can signal to hypothalamic regions involved in regulating feeding behavior.[37]

Along with the metabolic phenotypes of *Bmal1*$^{-/-}$ and *Clock*$^{\Delta 19}$ mutants, metabolic abnormalities seen in mice with targeted mutations of other clock genes *Pers* and *Crys* further support an intimate coupling of metabolic homeostasis and the circadian clock in adipose tissue. On a regular chow diet *Per2*$^{-/-}$ animals gradually loose body weight and decrease body fat content relative to wild-type controls. As mentioned before, *Per2* deficiency results in an over-activation of PPARγ target genes (*Ucp1*, *Cidea*) in adipose tissues which in turn augment lipid oxidation and energy expenditure.[45] In contrast, another study shows that when kept on a high fat diet *Per2*$^{m/m}$ animals are prone to increased body weight and higher adiposity which can be attenuated by restoring their feeding rhythms.[53] Differential responses to diet conditions were also described for *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mice. When fed a standard diet, *Cry1*$^{-/-}$*Cry2*$^{-/-}$ animals are underweight (and smaller) and show lower amounts of WAT due to higher energy expenditure and heat production compared with wild-type controls.[54] In contrast, under high-fat diet conditions *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mice gain significantly more weight and dramatically increase their fat content with no increase in food intake. *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mutants show hyperglycemia and hyperinsulinemia which may provoke elevated lipogenesis and triglyceride accumulation in WAT.[55] It is important to mention that in both strains impaired feeding rhythmicity is not a trigger of higher adiposity per se since on regular chow diet both *Per2*$^{m/m}$ and *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mutants display normal or lower body weight respectively, while feeding rhythms are already impaired.[53,55] Mice deficient for *Rev-erb*α develop higher adiposity on both regular chow and high fat diets supposedly due to increased *Lpl*-facilitated lipid uptake by adipose tissue.[35] Both single *Rev-erb*α$^{-/-}$ and behaviorally arrhythmic *Rev-erb*α/β double knockout mice display a shift of overall body metabolism to a more oxidative state with preferential usage of FFAs as energy substrate.[35,42] In contrast, *Ror*α$^{sg/sg}$ mutants are resistent to diet-induced obesity. This phenotype was attributed to defects in lipid production due to reduced expression of *SREBP-1c* in liver and increased oxidative metabolism in liver and adipose tissue.[56]

Circadian Disruption and Adipose Function

The SCN pacemaker synchronizes daily physiological activities such as sleep and food intake with cycling environmental conditions. Indeed, mice with SCN lesions lose diurnal rhythms in locomotor activity, energy expenditure, and food intake leading to increase in body weight and adiposity.[57] Moreover, certain

exogenous stimuli can perturb the biological clock and evoke metabolic dysbalance. For instance, high fat diet in itself is able to ameliorate behavioral and metabolic oscillations in wild-type mice and reduces the amplitude of clock gene expression in adipose tissue and other peripheral organs.[58] Interestingly, nighttime-restricted feeding can restore these manifestations and reduce body weight gain.[59]

Shifted light regimes (for instance during jet lag or shiftwork) are highly rampant in modern human society and interfere with the circadian clock, disrupt sleep patterns and promote obesity and diabetes.[60] In humans, forced desynchrony, i.e., adaptation to a behavioral 28-h cycle under controlled laboratory conditions, results in decreased blood leptin concentrations, increased glucose levels, and insulin resistance.[61] In line with this, chronic sleep restriction in mice increases food intake and leptin reduction during the light phase, and causes large changes in metabolic transcriptional programs in liver.[18] Of note, even a single night of sleep deprivation is able to phase shift the blood rhythm of visfatin (NAMPT) and elevate blood glucose.[38] Sleep duration in general is negatively correlated with body mass index (BMI) and adiposity. Short sleepers (below 6 h) show lower leptin and increased ghrelin levels—a combination that promotes appetite.[62,63]

Summary and Outlook

It becomes increasingly clear that circadian clocks and adipose function are tightly connected. Clock target genes in adipocytes include key regulators of lipogenesis, lipid breakdown, and adipokine function, balancing energy metabolism in adipose tissues and its communication with peripheral and central tissues over the course of the day. While research during the last years has focused on analyzing the molecular mechanisms by which circadian clocks impinge on adipose physiology, recent attempts to identify compounds capable of manipulating clock function at the cellular level may soon enable us to reprogram adipose chronophysiology to counteract its deleterious effects on energy homeostasis and adiposity-associated disorders in our 24/7 society.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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